Proposed Decision Memo for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndrome (CAG-00415N)

Decision Summary

CMS believes that that the evidence does not demonstrate that the use of allogeneic hematopoietic stem cell transplantation (HSCT) improves health outcomes in Medicare beneficiaries with myelodysplastic syndromes (MDS). Therefore, we are proposing that allogeneic HSCT for MDS is not reasonable and necessary under §1862(a) (1) (A) of the Social Security Act. However, we do believe the available evidence suggests that allogeneic HSCT for MDS is reasonable and necessary under §1862(a) (1) (E) of the Social Security Act through Coverage with Evidence Development (CED). Thus, we are proposing the following decision:

Allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes is covered by Medicare only in the context of a prospective controlled clinical study that meets the following standards:

A clinical study seeking Medicare payment for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome pursuant to Coverage with Evidence Development (CED) must address one or more aspects of the following questions.

1. Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?
2. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:

- relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

3. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:

    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR Parts 50 and 56.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

Proposed revisions to sections 110.8.1 of the NCD Manual are available in Appendix C.

We are requesting public comments on this proposed determination pursuant to section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO:	Administrative File: (CAG-00415N) Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome
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SUBJECT: Proposed Decision Memorandum for Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome
DATE: May 6, 2010

I. Proposed Decision

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II. Background

Myelodysplastic Syndrome (MDS) refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These bone marrow disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics.

Clinical Background and Burden of Disease

There are three "families" of cells commonly found in the blood: red cells, white cells, and platelets. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenia, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow. Most patients present with signs or symptoms of anemia (due to abnormally lowered red cell counts), which can be accompanied by infection (due to abnormally low white cell counts) and/or bleeding (due to abnormally low platelet counts). A persistently low blood cell count can necessitate the administration of frequent transfusions that over time may also have a decreasing positive impact for the patient, which is referred to as refractory cytopenia with transfusion dependency. Although some patients may not have any symptoms, most patients with MDS ultimately die from their low blood counts according to Nimer (2008).

Failure of the bone marrow to produce mature healthy cells is typically a gradual process; therefore MDS is not necessarily a rapidly terminal disease. Life expectancy may be measured in months to years and will vary considerably depending on the severity of the specific disorder, the patient’s ability to withstand treatment and the patient’s responsiveness to treatment. The worst case scenario is the transformation of MDS to acute myeloid leukemia (AML), which occurs in approximately thirty percent of patients with MDS (MDS Foundation Handbook, 2008). AML is an aggressive type of cancer that often fails to respond to treatment and has a high mortality rate. In addition, AML that is secondary to MDS is generally more resistant to treatment than AML that arises without a prior association with MDS (National Comprehensive Cancer Network [NCCN] guideline, 2009).

MDS becomes increasingly common with advanced age with an overall incidence of 3.3 per 100,000 and an incidence of between fifteen and fifty per 100,000 in patients over age 70. The median age at presentation is 76 years. Eighty percent of the total population receiving an MDS diagnosis is 65 years of age or older.

Classification of MDS

Because the disease course of MDS varies greatly from patient to patient, a number of diagnostic classification systems for grouping MDS "subtypes" have been developed over the years. The initial system, the French-American-British (FAB) classification, was developed in the early 1980s. The key criterion for diagnosis centered on the percentage of abnormal blast (i.e., precursor) cells in the bone marrow with a higher blast count signifying more aggressive disease. A blast count greater than 30 percent signifies a diagnosis of AML.

Diagnostic classification is based on examination of a bone marrow biopsy and, more recently, cytogenetics. Five subtypes of MDS were identified. Table 1 presents the FAB Classification of MDS as presented in the NCCN guideline, version 2, 2010.

TABLE 1: FAB[f] classification of MDS[g] (from the NCCN® Clinical Practice Guidelines in Oncology, Myelodysplastic Syndromes – v.2.2010, used with permission)

FAB subtype	% Peripheral blasts	% Bone marrow blasts
Refractory anemia (RA)	< 1	< 5
Refractory anemia with ringed sideroblasts (RARS)	< 1	< 5
Refractory anemia with excess blasts (RAEB)	< 5	5-20
Refractory anemia with excess blasts in transformation (RAEB-t)	$\geq$5	21-30
Chronic myelomonocytic leukemia(CMML) (> 1,000 monocytes/mcL blood)	< 5	5-20

[f] FAB = French-American-British
[g] Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol.1982; 51:189-199.
[h] WHO = World Health Organization

In 2001, the World Health Organization (WHO) expanded upon the FAB system by taking into account the number of types of abnormal "families" of blood cells, the presence or absence of certain cytogenetics abnormalities as well as by lowering the maximum allowable percentage of blast cells in the blood (Nimer, 2008). The WHO classification system was further updated in 2008 in order to incorporate new scientific and clinical information and to add new diseases (NCCN guideline, 2009). The maximum blast count required for AML was reduced to twenty percent. Table 2 presents the 2008 WHO Classification of MDS as presented in the NCCN guidelines.

TABLE 2: Classification Systems for *de novo* MDS: 2008 WHO[h] Classification of MDS[i](from the NCCN® Clinical Practice Guidelines in Oncology, Myelodysplastic Syndromes – v.2.2010, used with permission)

Subtype	Blood	Bone marrow

Subtype	Blood	Bone marrow
Refractory cytopenia with unilineage dysplasia (RCUD) [j]	Single or bicytopenia	Dysplasia in ≥ 10 % of one cell line, < 5% blasts
Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	≥ 15 % of erythroid precursors w/ring sideroblasts, erythroid dysplasia only, < 5 % blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s): < 1 x 109/L monocytes	Dysplasia in ≥ 10 % of cells in ≥2 hematopoietic lineages, ± 15 % ring sideroblasts, < 5 % blasts;
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s): ≤ 2-4 % blasts, < 1 x 10 9/L monocytes	Unilineage or multilineage dysplasia, No Auer rods, 5 % to 9 % blasts
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s): 5-19 % blasts, < 1 x 10 9/L monocytes	Unilineage or multilineage dysplasia Auer rods ±, 10 % to 19 % blasts
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias	

Subtype	Blood	Bone marrow
		Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, < 5% blasts
MDS associated with isolated del (5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del 5(q), < 5 % blasts

[i] Brunning R, Orazi A, Germing U, et al. Myelodysplastic Syndromes, Chapter 5, in Swerdlow S, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue, 4th edition. IARC Press, 2008, p88-103.
[j] This category encompasses refractory anemia (RA), Refractory Neutropenia (RN) and Refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS Unclassified.

TABLE 3: Classification Systems for *de novo* MDS: Myelodysplastic/Myeloprolifierative Neoplasms (MDS/MPN) WHO Classification[k] (from the NCCN® Clinical Practice Guidelines in Oncology, Myelodysplastic Syndromes – v.2.2010, used with permission)

Subtype	**Blood**	**Marrow**
Chronic myelomonocytic leukemia-1 (CMML-1)	>1x109/L monocytes, <5% blasts	Dysplasia in 1 hematopoietic line, <10% blasts
CMML-2	>1x109/L monocytes, 5-19% blasts or Auer rods	Dysplasia in 1 hematopoietic line, 10-

Subtype	Blood	Marrow
		19% blasts or Auer rods
Atypical chronic myeloid leukemia (CML), Bcr-Abl 1 negative	WBC 13x109/L, neutrophil precursors >10%, <20% blasts	Hypercellular, <20% blasts
Juvenile myelomonocytic leukemia (JMML)	>1x109/L monocytes, <20% blastsl	>1x109/L monocytes, <20% blastsl
MDS/MPN, unclassifiable ('Overlap syndrome')	Dysplasia + myeloproliferative featuresm , No prior MDS or MPN	Dysplasia + myeloproliferative features

Acute myeloid leukemia with myelodysplasia-related changes[n]
WHO Classification[o]
1. AML post MDS or MDS/MPN
2. AML with an MDS-related cytogenetic abnormality
3. AML with multilineage dysplasia

[k] Orazi A, Bennet JM, Germing U, et al, Myelodysplastic/Myeloproliferative Neoplasms, Chapter 4, in Swerdlow S, Campo E, Harris NL, et al. (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 76-86.
[l] Ph negative plus 2 features: Hb F, PB immature myeloid cells, WBC >10x109/L, clonal chromosomal abnormality, GM-CSF hypersensitivity in vitro, for example, thrombocytosis, leukocytosis, splenomegaly.
[n] Greater than 20% blasts in PB or marrow. Some cases with 20-29% blasts, especially if arising from MDS, may be slowly progressive and may behave more similar to MDS (RAEB-t by FAB classification) than to overt AML.
[o] Arber DA, Brunning RD, Orazi A, et al. Acute myeloid leukaemia with myelodysplasia-related changes, In Chapter 6, Acute Myeloid Leukemia and Related Precursor Neoplasms, in Swerdlow S, Campo E,Harris NL, et al. (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 124-126.

Although the revisions to the FAB system and hence the resultant WHO diagnostic classification system are considered to be an improvement, the 2009 NCCN guideline states that "the NCCN MDS panel members currently endorse reporting and using both the FAB and the WHO classification systems" in clinical practice. Similarly, when evaluating clinical studies and comparing results across those studies it is important to note whether patients were diagnosed with the FAB or WHO classification system.

Due to the highly variable nature of the patient population with regards to MDS subtype, severity of disease and baseline medical condition, the clinical management of a patient with MDS is highly individualized and can range from solely supportive care with periodic transfusions and antibiotics to intensive chemotherapy with or without transplantation. The International Prognostic Scoring System (IPSS) is the classification scheme widely recognized and used in determining the most suitable treatment regimen.

The IPSS scheme, as first described in Greenberg, et al. (1998), is the worldwide system used for risk-based grading of the severity and progression of MDS and for ascertaining the patient's prognosis. The goal of the IPSS is to determine, for a given MDS subtype, the patient's chance for survival and the risk for MDS to transform (i.e., progress) to AML (NCCN guideline, 2009). The authors found that three major variables (marrow blast percentage, number of cytopenias and cytogenetics subgroup) could determine the outcome; a risk score was assigned to each. Four risk groups with regards to survival and progression to AML were then created by combining the risk scores for the three major variables.

Table 4 presents the IPSS Classification system as presented in the 2009 NCCN guideline.

TABLE 4: IPSS (IPSS [p,q]) Classification System (from the NCCN® Clinical Practice Guidelines in Oncology, Myelodysplastic Syndromes – v.2.2010, used with permission).

	Survival and AML evolution Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0

	Survival and AML evolution Score value				
Marrow blasts (%)r	< 5	5-10	-	11-20	21-30
Karyotype s	Good	Intermediate	Poor		
Cytopenia t	0/1	2/3			

Risk category (% IPSS pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1

HIGH (7)	≥2.5	0.4	0.2

[p] IPSS = International Prognostic Scoring System.
[q] This research was originally published in Blood. Greenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088; Erratum. Blood 1998;91:1100. © The American Society of Hematology.
[r] Patients with 20-30 % blasts may be considered as MDS or AML.
[s] Cytogenetics: Good = normal, -Y alone, del (5q) alone, del (20q) alone; Poor = complex (3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. [This excludes karyotypes t(8;21), inv16, and t(15;17), which are considered to be AML not MDS.]
[t] Cytopenias: neutrophil count <1,800/mcL, platelets < 100,000/mcL, Hb < 10g/dL.

Tables 1-4 are reproduced with permission from The NCCN 2.2010 Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology. Copyright National Comprehensive Cancer Network, 2010. Available at: http://www.nccn.org. Accessed February 23, 2010) To view the most recent and complete version of the guideline, go online to www.nccn.org.

Overall, the Low and Intermediate-1 categories are associated with a longer median survival and a lower chance for progression to AML; these 2 categories comprise the low risk group. The Intermediate-2 and High categories are associated with a shorter median survival and a higher chance for progression to AML and comprise the high risk group.

Much like the diagnostic classification system, the IPSS prognostic system continues to evolve. The original IPPS was created using study data from patients who were diagnosed with the FAB classification.

To acknowledge the introduction of the WHO classification, in 2005, Malcovati, et al. performed analyses to determine the prognostic potential when using study data from patients diagnosed with the WHO classification (Malcovati et al., 2005). The impact of red blood cell transfusion dependency on overall survival and survival free of leukemia (i.e., progression to AML) was also examined although a definition of transfusion dependency was not provided. The resultant system is referred to as the WHO Prognostic Scoring System (WPSS).

The authors found that the overall survival of patients who are dependent on red blood cell transfusions was statistically significantly shorter than for non-transfusion dependent patients. Survival free of AML was also statistically significantly shorter for patients with transfusion dependency than for patients without red blood cell transfusion dependency. Hence, the authors found that the persistent requirement for red blood cell transfusions is a negative prognostic factor for patients with MDS (Malcovati et al., 2005).

In 2008, Kao et al. expanded on this finding by examining the impact of the severity of a low red cell count on overall survival and time to evolution to AML. The authors found that the overall survival worsened and time to AML shortened as the blood count worsened (defined as a hemoglobin level of less than 10 grams /deciliter). After multivariate analysis, the red blood cell count was determined to add useful prognostic value with regards to overall survival but not with regards to time to progression to AML.

Typically a physician applies the FAB or WHO classification and the IPSS category as part of recommending a treatment plan. The type of plan will be based on the patient's overall health but also on the extent to which symptoms can be relieved, blood abnormalities reduced and AML progression minimized (MDS Foundation Handbook, 2008).

Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is a procedure in which stem cells are taken from a person's bone marrow or blood and then administered to the patient by intravenous infusion. When the stem cells come from a donor, the procedure is called an allogeneic HSCT. Allogeneic HSCT is believed by some to be the only potential cure for patients with MDS.

HSCT has traditionally been limited to patients younger than 55 or even fifty years of age. This is because of the increase in medical problems (a.k.a., comorbidities) and the general decline in overall health status that commonly occur as a person ages. For example, older patients have greater difficulty tolerating intensive (a.k.a., myeloablative) chemotherapy either with or without subsequent transplantation. The advent of nonmyeloablative chemotherapy and reduced–intensity chemotherapy (RIC) regimens prior to transplantation has significantly increased the potential for patients with MDS who are older than 55 years to receive HSCT (Alyea, et al., 2005). The attractiveness of RIC prior to transplant is "the lower incidence of side effects, which means the treatment will be better tolerated by the older patient, and the patient may have greater chance of a successful transplant." (MDS Foundation Handbook, 2008)

III. History of Medicare Coverage

CMS does not have a national policy that specifically addresses coverage of allogeneic HSCT for MDS.

Section 110.8.1 of the National Coverage Determination (NCD) Manual

(http://www.cms.gov/manuals/103_cov_determ/ncd103c1_Part2.pdf) governs national coverage and noncoverage of Stem Cell Transplants, as described below.

Indications and Limitations of Coverage

1. Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion.

a. Covered Indications

   The following uses of allogeneic bone marrow transplantation are covered under Medicare:

   - Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary; and
   - Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID), and for the treatment of Wiskott-Aldrich syndrome.

b. Noncovered Indications

   - Effective for services performed on or after May 24, 1996, allogeneic stem cell transplantation is not covered as treatment for multiple myeloma.

In the absence of a national coverage determination, contractors have the discretion to determine coverage for allogeneic HSCT for all other indications through the local coverage determination (LCD) process or by individual claim by claim adjudication.

Current request

CMS opened this NCA based on a request from the following groups: The National Marrow Donor Program, American Society for Blood and Marrow Transplantation, American Cancer Society, American Cancer Society Cancer Action Network, AABB, American Society of Hematology, American Society of Clinical Oncology, Aplastic Anemia and MDS International Foundation, Blood and Marrow Transplant Information Network, National Bone Marrow Transplant Link, The Bone Marrow Foundation and The Leukemia and Lymphoma Society. In their formal letter, the requestors asked for national coverage of allogeneic HSCT for Medicare beneficiaries "who would either be at high risk for progression to leukemia or be at risk for MDS complications that place them at high risk for death or prevent the future possibility of a transplant."

On November 10, 2009, CMS accepted this formal request from several bone marrow and cancer organizations and societies and the first public comment period opened. A list of articles submitted by the requestor is included in Appendix B.

Benefit Category

Medicare is a defined benefit program. A prerequisite for Medicare coverage is that an item or service must meet one of the statutorily defined benefit categories in the Social Security Act and not otherwise be excluded from coverage.§1812 (Scope of Part A); §1832; (Scope of Part B); §1861 (s) (Definition of Medical and Other Health Services).

CMS has determined that autologous and allogeneic stem cell transplantation fall within the benefit categories of inpatient hospital services under Part A and physicians' services under Part B. See §1812 (a) (1) (inpatient hospital services); §1832 (outpatient hospital services incident to a physician's service); §1861(s) (2) (incident to physician's services); §1861(b) (inpatient hospital services).

IV. Timeline of Recent Activities

November 10, 2009	CMS accepts formal NCD request for coverage of the allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome. The tracking sheet is posted and the initial 30-day comment period begins.
December 10, 2009	Initial 30 day public comment period closes. Comments are posted on the website.

V. FDA Status

Hematopoietic stem/progenitor cells (HPC) for transplantation are regulated as human cells, tissues, and cellular-and tissue based products (HCT/Ps) by FDA under 21 CFR §1271. Section 1271.3(d) defines human cells, tissues, or cellular or tissue-based products (HCT/Ps) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. Examples of HCT/P include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem /progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue."

The regulatory approach to HCT/Ps, including HPC, distinguishes among autologous products, allogeneic products from first- or second-degree relatives, and allogeneic products form unrelated donors. HCT/Ps that meet all of the criteria set forth in 21 CFR S§1271.10(a) are regulated solely under section 361 of the PHS Act and the regulations in Part 1271, and no FDA premarket review is required. To satisfy these criteria, a HCT/P must:

- be minimally manipulated;
- be intended for homologous use only;
- not be combined with another article (with some limited exceptions); and
- not have a systemic or metabolic effect; or if it does, must be intended for autologous use or use by a first- or second-degree blood relative.

HCT/Ps that do not meet all of these criteria are also regulated as drugs, devices, and/or biological products, and require FDA premarket review. Section 1271.3(a) defines the term autologous use as "the implantation, transportation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." Section 1271.3(c) defines the term homologous use as "the replacement or supplementation of a recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor."

VI. General Methodological Principles

When making national coverage decisions under section 1862(a) (1) (A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

VII. Evidence

A. Introduction

The purpose of this national coverage analysis (NCA) is to determine if the evidence is sufficient to conclude that beneficiaries with MDS experience improved health outcomes with HSCT compared to beneficiaries with MDS whose management does not include HSCT.

This NCA does not focus on any particular subtype of MDS. As noted in the Background section of this NCA, MDS refers to a group of blood disorders. Each subtype of MDS has a distinct presentation and prognosis. The underlying cause for the disease, the types and severity of abnormal blood counts and the potential for progression to AML are different for each subtype.

Similarly, HSCT is a procedure that involves numerous steps and medical interventions that in sum lead to a complex set of medical decisions and procedures over a span of months. Some examples of these numerous and complex aspects include the use of: related versus unrelated matched donor; allogeneic versus autologous donor; bone marrow versus peripheral blood-sourced cells; one type of chemotherapeutic agent versus another type; standard myeloablative versus non-myeloablative versus reduced-intensity conditioning; the use of induction chemotherapy versus not; and the specific types and doses of agents used for graft versus host disease (GVHD) prophylaxis.

CMS recognizes that each certified transplantation center in the U.S. develops a clinical treatment protocol that can vary to some degree from other centers but which adheres to standards of excellence set by clinical experts in the field of transplantation medicine, surgery, nursing and pharmacy. The Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation (JACIE) was established in 1999. Both the National Marrow Donor Program (NMDP) and the Foundation for the Accreditation of Cellular Therapy (FACT) and the JACIE (jointly referred to as the FACT-JACIE) which have established provider and facility standards for conducting HSCT, serve to bolster, support and oversee these standards of excellence. In addition, Congressionally-mandated data collection of the results of HSCT, which is conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR), further serves to strengthen and improve the processes involved with performing HSCT.

CMS generally focuses its review on evidence that includes patients who are 65 years of age or older. The typical Medicare beneficiary is 65 years of age or older; however, a relatively small percentage of beneficiaries may be younger than 65 year old due to Medicare entitlement based on other factors such as end stage renal disease or disability.

However, CMS acknowledges that traditionally HSCT was routinely contraindicated in patients with MDS who were older than 55 or even 50 years of age due to the patient’s inability to tolerate the standard myeloablative conditioning regimen. The literature, therefore, is still dominated by evidence generated in patients younger than 65 years of age. This is slowly changing with the relatively recent introduction of non-myeloablative conditioning (NMA) and reduced-intensity conditioning (RIC) regimens for patients with MDS who are older than 65 years or who have other contra-indications to HSCT.

There is considerable morbidity and mortality associated with some subtypes of MDS as well as with HSCT. The greater chance for non relapse mortality (NRM) or transplant-related mortality (TRM) with the use of standard myeloablative conditioning prior to transplantation has traditionally limited transplantation to nonelderly and nondebilitated patients (Martino, et al., 2006). Thus, the primary outcomes of interest in this NCA are overall survival (OS), progression-free survival (PFS) and TRM or NRM.

Literature Search

On February 4, 2010, CMS performed a PubMed search of the clinical literature using the following search terms: "myelodysplastic syndrome" or "MDS" and "transplant." The limitations used were: Human, English, Aged (65+ years), Publication Date (2000 to present) and Article type (Clinical Trial, Randomized Clinical Trial, Meta-analysis).

B. Discussion of evidence reviewed

1. Question

Is the evidence adequate to conclude that beneficiaries with a diagnosis of MDS would experience improved health outcomes with a HSCT compared to beneficiaries whose management does not include HSCT?

2. External technology assessment

CMS did not commission an external technology assessment on this topic.

3. Internal technology assessment

Results from the CMS literature search as well as the literature articles submitted by the requestors and the literature references provided by public commenters were considered for the internal technology assessment (TA). The CIBMTR Progress Report for calendar year 2008 was reviewed to find a listing of published articles based on research performed on the CIBMTR database. In addition, an Internet search was performed to identify any available evidence-based guidelines and professional society position statements.

From the above evidence sources, CMS looked for published, peer-reviewed full articles (i.e., not abstracts) of controlled clinical trials that provided results on the use of HSCT versus other therapies in the clinical management of patients with MDS of any subtype. Emphasis was placed on articles that presented evidence in the Medicare population (i.e., 65 years of age or older).

Articles that provided background information on MDS (e.g., epidemiology), a study that did not investigate HSCT (e.g., a study that examined the safety and/or efficacy of a chemotherapeutic agent) or a non-clinical study (i.e., animal research) were not included in this internal technology assessment

4. Evidence Summary

Cutler CS, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low -risk myelodysplasia is associated with improved outcome. Blood2004; 104:579-585.

The authors performed a decision analysis to investigate the optimal timing for bone marrow transplantation for patients with MDS. There were two MDS data sources for the analysis: the International MDS Risk Analysis Workshop (IMRAW) database was the source for the nontransplantation cohort (n= 184); the International Bone Marrow Transplant Registry (IBMTR; n= 193)) and the Fred Hutchinson Cancer Research Center (n= 67) databases were the sources for the MDS transplantation cohort. IBMTR was the one AML data source (n= 230). All patients had received myeloablative conditioning.

Three possible transplantation strategies were tested using a Markov decision model: 1) transplantation at time of MDS diagnosis; 2) transplantation at time of progression to AML; 3) transplantation at a fixed time interval after diagnosis. Analyses were performed for all four IPSS risk groups. A base case was used consisting of a 35 year old man with newly diagnosed MDS and an available HLA-matched sibling donor.

All patients were sixty years old or younger. The median age in the nontransplantation cohort was 49.8 years while the median age in the various transplant groups was 39.4 to 45.6 years. In the nontransplantation group, the majority (73.9%) had an IPSS Low or Intermediate-1 risk profile. In the transplantation group, the majority (75%) had an IPSS Intermediate-1 or Intermediate-2 profile.

The outcomes results are reported in tables 5-8 below.

TABLE 5: Median survival in months according to transplantation status (from Cutler, et al., 2004).

	Nontransplantation Cohort	Transplantation Cohort
Median Survival (months)	62.9	14
Significance not stated		

TABLE 6: Median survival in months and 25% AML transformation time by IPSS risk group for the nontransplantation cohort (from Cutler, et al., 2004).

IPSS	Low	Intermediate-1	Intermediate-2	High

Median Survival (months)	141.1	62.9	22.5	4.9
25 % AML transformation time		84.6	19.2	2.7
All differences P< 0.001				

TABLE 7: Median survival in months according to IPSS risk group for the transplantation cohort (from Cutler, et al., 2004).

IPSS	Low	Intermediate-1	Intermediate-2	High
Median Survival (months)	40.2	20.5	14.8	6.1
All differences P = 0.04				

TABLE 8: Discounted life expectancy, in years, for alternative transplantation strategies (from Cutler, et al., 2004).

	Discounted life expectancy (yrs)					
IPSS	Transplantation at diagnosis	Transplantation at a fixed time point				Transplantation at AML progression
		2 yr	4 yr	6 yr	8 yr	
Low	6.51	6.86	7.47	7.46	7.49*	7.21
Intermediate-1	4.61	4.74	4.72	5.02	5.20*	5.16
Intermediate-2	4.93*	3.21	2.94	2.85	2.84	2.84
High	3.20*	2.75	2.75	2.75	2.75	2.75

* Dominant strategies

The authors concluded that "delayed transplantation for IPSS Low and Intermediate-1 risk groups is associated with maximum discounted life years" while for the IPSS Intermediate-2 and High risk groups "transplantation at the time of diagnosis is associated with maximization of discounted life years." They also hypothesized that for the IPSS Low and Intermediate-1 risk groups the optimal timing of transplantation "is at the time of the development of a new cytogenetics abnormality, the appearance of a clinically important cytopenia, or the progression from one IPSS group to a higher risk group."

Martino R, et al.Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood2006; 108:836-846.

A retrospective, multicenter study was performed to evaluate myeloablative conditioning versus reduced-intensity conditioning (RIC) prior to HSCT in patients with MDS or AML. Disease relapse, progression-free survival, overall survival and nonrelapse mortality were among the outcomes studied.

Myeloablative conditioning was administered to 621 patients with MDS while 215 patients with MDS received RIC. Sixty-three percent of the patients who received myeloablative conditioning had MDS while 59% of the patients who received RIC had MDS. Of the fifty percent of patients for whom the authors could collect IPSS-related information, 66% who received myeloablative conditioning had high risk MDS and 69% who received RIC had high risk MDS. Twenty-seven percent of patients who received myeloablative conditioning were older than fifty years and 73% of the patients who received RIC were older than 50 years.

The outcomes results are reported in tables 9-12. After each table is a report of the results of a multivariate analysis for that outcome.

TABLE 9: Incidence of nonrelapse mortality (from Martino, et al., 2006).

	Myeloablative	RIC
% Nonrelapse mortality (95% CI)		
3-month	0.20 (0.17-0.23)	0.15 (0.11-0.21)
1-year	0.28 (0.25-0.32)	0.20 (0.15-0.26)
3-year	0.32 (0.28-0.36)	0.22 (0.17-0.28)
P = 0.04		

Multivariate analysis of 3-year nonrelapse mortality showed that the use of RIC reduced nonrelapse mortality (HR, 0.61, 95%CI, 0.41-0.91; p = 0.015) compared to myeloablative conditioning and that patient age older than fifty years increased the nonrelapse mortality compared to patient age fifty and younger (HR, 1.4 , 95%CI, 1.1-1.8; p = 0.04).

TABLE 10: Incidence of disease progression/relapse (from Martino, et al., 2006).

	Myeloablative	RIC
% Disease progression/relapse (95% CI)		
3-month	0.08 (0.06-0.10)	0.14 (0.11-0.20)
1-year	0.22 (0.19-0.25)	0.35 (0.30-0.43)
3-year	0.27 (0.24-0.31)	0.45 (0.38-0.53)
P < 0.01		

Multivariate analysis of 3-year disease progression/relapse showed that the use of RIC increased disease progression/relapse (HR, 1.64, 95%CI, 1.2-2.2; p= 0.001) compared to myeloablative conditioning; and that an advanced stage of disease increased disease progression/relapse compared to an early stage of disease (HR, 2.2, 95%CI, 1.2-4.1; P= 0.01).

TABLE 11: Incidence of progression-free survival (from Martino, et al., 2006).

	Myeloablative	RIC
% Progression-free survival (95% CI)		
3-month	0.72 (0.74-0.80)	0.76 (0.69-0.81)
1-year	0.50 (0.46-0.54)	0.45 (0.38-0.52)
3-year	0.41 (0.37-0.45)	0.33 (0.27-0.40)
P = 0.1		

Multivariate analysis of 3-year progression-free survival showed that the use of RIC did not impact the progression-free survival compared to myeloablative conditioning; and that a diagnosis of MDS increased the progression-free survival compared to a diagnosis of secondary AML (HR, 0.78, 95%CI, 0.6-0.98; p= 0.03). There was a trend toward a decrease in progression-free survival in patients older than fifty years compared to patients fifty years or younger.

TABLE 12: Overall survival (from Martino, et al., 2006).

	Myeloablative	RIC
% Overall survival (95% CI)		
3-month	0.82 (0.79-0.85)	0.84 (0.79-0.89)
1-year	0.58 (0.54-0.62)	0.57 (0.49-0.63)
3-year	0.45 (0.41-0.49)	0.41 (0.35-0.47)
P = 0.7		

Multivariate analysis of 3-year overall survival showed that the use of RIC did not impact overall survival compared to myeloablative conditioning; that patient age older than fifty years decreased the overall survival compared to patient age fifty and younger (HR, 1.3, 95%CI, 1.05-1.6); p= 0.02); and that a diagnosis of MDS increased overall survival compared to a diagnosis of secondary AML (HR, 0.72, 95%CI, 0.57-0.92; p= 0.007)./p>

The authors concluded that "the reduction in 3-year NRM after a heterogeneous group of RIC indicates that the goal of reducing early NRM with RICs has been accomplished, but at the cost of a significantly higher risk of relapse." The authors continue to state that RIC needs further study, especially that "different RIC approaches should be compared in detail, since the alkylating agent dose intensity and the use of monoclonal antibodies may have an impact on transplantation outcome."

Laport GG, et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. Biology of Blood and Marrow Transplantation2008; 14:246-255.

This was a prospective, multi-center study of 148 patients with MDS, AML, CMML or myeloproliferative disease who received allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. All patients were considered to be at high risk to receive myeloablative conditioning due to age, co-morbidities or prior history of transplantation. Given the multi-center nature of the study, various transplantation protocols were used. The protocols primarily differed in the use of HLA-matched versus unrelated donors, duration and intensity of graft versus host disease treatment and the specific type of agents used for conditioning. Patients had to be less than 75 years old. Outcomes studied were nonrelapse mortality, relapse/progression, relapse-free survival and overall survival.

Patients with MDS were stratified by IPSS risk group: Low/Intermediate-1 and Intermediate-2/High. Forty patients had *de novo* MDS. Median age was sixty years with a range of 42 to 72. Twenty of these patients were sixty years of age or older. Twenty-two patients (56%) were in the Low/Intermediate-1 risk group.

These forty patients with *de novo* MDS had no significant differences in relapse-free survival or non-relapse mortality between the Low/Intermediate-1 and Intermediate-2/High groups. The Intermediate-2/High group had a significantly higher incidence of relapse/progression compared to the Low/Intermediate-2 group (HR, 2.92, 95%CI, 1.0-8.6; p=0.04). In multivariate analysis, a significantly decreased relapse risk was associated with complete remission at the time of transplantation. The results in these forty patients were not reported by age.

The authors' conclude that, "Allogeneic HCT remains the only curative modality for MDS and MPD, with non-myeloablative conditioning or RIC regimens clearly benefiting this older population by reducing toxicity. However, further investigation is warranted to determine the optimal regimen with adequate dose intensity and low toxicity."

Oliansky DM, et al. The role of cytoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: An evidence-based review. Biology Blood Marrow Transplant 2009; 15:137-172.

The American Society for Blood and Marrow Transplantation (ASBMT) sponsored a systematic review of the medical literature for the use of allogeneic HSCT in patients with MDS. A steering committee was convened to invite and oversee an independent panel of disease experts to conduct the systematic review and make treatment recommendations based on the evidence. The review article was published in *Biology of Blood and Marrow Transplantation*, which is the journal of the ASBMT (Oliansky, et al., 2009). Of note, ASBMT was one of the requestors for this NCD.

The authors performed a PubMed and Medline search on January 17, 2007 using the search terms "myelodysplastic syndrome" or "MDS" plus "transplant." The search was limited to "human trials," "English language" and publication date of 1990 or later. There were two subsequent updated searches with the last update performed on April 15, 2008. Only articles that were peer-reviewed and presented the results of Phase two or three studies with 25 or more patients with MDS who were fifteen years of age or older were included in the systematic review. If the study evaluated patients with AML as well as *de novo* MDS, then at least sixty percent of the patients had to have had *de novo* MDS or the study results had to have been stratified by disease category.

The authors graded the quality of the study design used in as well as the strength of the evidence from each article (Table 13). The authors also graded the strength of the treatment recommendation presented in each article (Table 14).

TABLE 13: Grading the Quality of Study Design and the Strength of the Evidence (from Oliansky, et al., 2009).

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCT with very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal.
2-	Case-control or cohort studies case-control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g., case reports, case series)

4	Expert opinion

RCT= randomized controlled trial

TABLE 14: Grading the Strength of the Treatment Recommendation (from Oliansky, et al., 2009).

A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

RCT= randomized controlled trial

The authors assessed 46 articles that each typically focused on only one of a variety of clinical aspects of performing HSCT including: timing of transplantation, pre-HSCT induction chemotherapy, donor selection and transplantation techniques including reduced-intensity conditioning versus high dose conditioning.

Three tables were presented that supplied the study design/methodology and results for each of the 46 articles. These tables are not reproduced in this NCA but can be found in the publication by Oliansky, et al, (2009). To briefly summarize: across all studies the study design/methodology ranged from single site to multi-center, from retrospective to prospective and from uncontrolled to controlled. Various combinations of therapies (pharmaceutical agents, biologicals, radiation therapy) were used for chemotherapy (for conditioning, consolidation and/or induction) and for treating or preventing graft versus host disease.

The study population was typically comprised of patients with MDS and secondary AML but could also include patients (in varying proportions) with CMML, myeloproliferative neoplasms or acute lymphocytic leukemia. The median age of the patients ranged from 24 to 62.8 years; the youngest patient was 1 year old and the oldest patient was 73 years old.

Except for the footnotes and the column indicating the references, Table 15 fully reproduces the summary of the results and recommendations from the authors.

TABLE 15: Summary of Treatment Recommendations Made by the Expert Panel for MDS (from Oliansky, et al., 2009).

Indication for SCT	Treatment recommendation grade	Highest level of evidence	Treatment Recommendation Comments

Timing of transplantation	C	2+	Early SCT recommended for patients with IPSS score of INT-2 or high risk at diagnosis, who have a suitable donor and meet the transplant center's eligibility criteria, and for selected patients with a Low or INT-1 risk IPSS score at diagnosis who have poor prognostic features not included in the IPSS (i.e., older age, refractory cytopenias, etc.)
Pre-SCT induction chemotherapy	No recommendation	2++	In absence of RCTs there are insufficient data to make a treatment recommendation for or against pre-SCT induction chemotherapy. The decision to use pre-SCT induction therapy should be made on an individual basis.
DONOR SELECTION			
Related v. unrelated allogeneic SCT	No recommendation	2+	There is no evidence of a survival advantage based on donor relation. In clinical practice, matched related donor allogeneic SCT is recommended if available. If a matched related donor is not available, an unrelated donor allogeneic SCT may provide equivalent outcomes. The published data do not reflect the selection of donors on the basis of molecular HLA typing.
Related, unrelated, either, or unspecified allogeneic SCT	B	2++	There are sufficient data demonstrating a long-term curative outcome for related and unrelated allogeneic SCT.

Autologous v. allogeneic SCT	C	2++	Based on data and expert opinion, an HLA-matched allogeneic donor (sibling, other family member, unrelated individual or cord blood) SCT is recommended if an appropriate donor is available. If an allogeneic donor is not available, and CR is achieved with induction therapy, an autologous SCT can be considered in the context of a clinical trial.
TRANSPLANTATION TECHNIQUES			
BMT v. PBSCT Allogeneic BMT v. PBSCT	B	1+	For low-risk disease, allogeneic PBSCT and BMT from related donors have equivalent outcomes. Based on one study, patients with high-risk disease may have a survival advantage with related donor allogeneic PBSCT.
	No recommendation		There is insufficient evidence to recommend bone marrow v. peripheral blood for unrelated donor allogeneic SCT.
Autologous BMT v. PBSCT	No recommendation	2+	There is no evidence of a survival advantage based on stem cell source.

Conditioning Regimen Comparison Reduced intensity v. high dose intensity conditioning	No recommendation	2++	There are insufficient data to make a recommendation for optimal conditioning regimen intensity. A range of dose intensities is currently being investigated and the optimal approach will likely depend on disease and patient characteristics such as age and comorbidities.
Comparison of ≥ 2 high-dose regimens	No recommendation	2++	There are insufficient data to make a recommendation. There is no evidence of a survival advantage with any one high dose conditioning regimen.

SCT= stem cell transplantation; RCT= randomized controlled trial; CR= complete remission; RCT= randomized clinical trial; PBSCT= peripheral blood stem cell transplantation; BMT= bone marrow transplantation; HLA= human leukocyte antigen; IPSS= International Prognostic Scoring System; INT= intermediate

To summarize Table 15, for patients with IPSS High risk disease the authors recommended that HSCT be performed soon after diagnosis if a suitable donor is available and the patient meets the eligibility criteria of a transplant center. The source of the stem cells may be from either a related or an unrelated donor since the evidence showed that a "long-term curative outcome" after allogeneic HSCT is associated with either source. The evidence also suggested that there may be a greater chance of patient survival when the stem cells come from the peripheral blood of a related donor. The recommendations are based on B and C strength evidence, which results from an overall body of evidence that the authors rated as having a quality of 2+ to 2++.

For patients with IPSS Low risk disease at the time of diagnosis the authors recommended that HSCT be performed soon after diagnosis for "poor prognostic features not included in the IPSS" such as older patient age or disease that is not responding to treatment. Just as with IPSS High risk patients, the source of the stem cells may be from either a related or an unrelated donor; however, the evidence showed equivalent clinical results when the stem cells come from either the peripheral blood or the bone marrow of a related donor.

The authors noted that currently there is insufficient evidence regarding the optimal conditioning regimen, whether it is a high-intensity or a low-intensity regimen, and that the selection of a conditioning regimen should be tailored to the individual patient based on disease and patient characteristics.

In their discussion the authors noted a number of limitations in their systematic review. One limitation was the lack of trials that compare the use of HSCT versus non-HSCT regimens. The authors stated that this is because patients with an available donor typically receive HSCT since only HSCT offers a chance of cure for patients with MDS.

The authors also noted that the inevitable and steady progression of medical technology and clinical management since 1990 (the start date for the systematic review's search criteria) likely impacted the quality of the review by introducing considerable variability amongst the studies reviewed for the systematic review.

McClune BL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. Journal of Clinical Oncology2010; published ahead of print on March 8, 2010 at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.25.4821.

This was a retrospective analysis of the CIBMTR database (from 1995 to 2005) on 1080 patients from 148 centers who received a HSCT that was preceded by either reduced-intensity conditioning (RIC) or non-myeloablative (NMA) conditioning.

The cytogenetic profile for MDS was listed as good, intermediate or poor risk based on the IPSS however actual IPSS scores were not available. For the analysis MDS was classified as either "early" (refractory anemia, acquired idiopathic sideroblastic anemia or pre-HSCT marrow blast count of less than five percent) or "advanced" (refractory anemia excess blasts, refractory anemia excess blasts in transformation, chronic myelomonocytic leukemia or marrow blast count greater than or equal to five percent). The patients were divided into four groups based on age: forty to 54, 55 to 59, 60 to 64 and greater than or equal to 65 years. The primary outcomes were overall survival, disease-free survival, nonrelapse mortality and hematologic relapse.

Of the 1080 total patients, 535 had MDS. The age range was forty to 78 years. The median age in the greater than or equal to 65 years age group was 67 years. Only one patient had a good cytogenetic profile; the majority had an intermediate profile. The majority of patients in each age group had advanced disease.

The outcomes are reported in tables 16-19. After each table is a report of the results of a multivariate analysis for that outcome.

TABLE 16: Non-relapse mortality for patients forty years of age and older who received HSCT for MDS according to age group (from McClune, et al., 2010).

	40-54 years	55-59 years	60-64 years	65 years and older
% Non-relapse mortality (95% CI)				
100-days	17 (12-22)	17 (12-24)	13 (8-20)	19 (10-30)
1-year	29 (23-36)	32 (25-40)	32 (24-40)	35 (22-48)
2-year	33 (27-40)	39 (31-47)	35 (27-44)	39 (26-53)

No statistically significant differences seen.				

Multivariate analysis was performed for both MDS and AML combined. The one-year non-relapse mortality was adversely affected by a lower Karnofsky Performance Score (i.e., a more debilitated patient), a diagnosis of MDS (regardless of cytogenetic profile) and a worsening HLA disparity (statistical significance not provide). Patient age did not impact non-relapse mortality. Use of a non-myeloablative conditioning regimen was associated with a borderline lower risk of non-relapse mortality (OR, 0.75, 95%CI, 0.57 - 1.0; p=0.05). The most common reason for death for both MDS and AML patients was relapse (33%) followed by infection (21%).

TABLE 17: Relapse at 2 years for patients forty years of age and older who received HSCT for MDS according to age group (from McClune, et al., 2010).

	40-54 years	55-59 years	60-64 years	65 years and older
%Relapse at 2 years (95% CI)				
	28 (22-34)	29 (22-37)	29 (21-38)	25 (14-38)
No statistically significant differences seen.				

Multivariate analysis was performed for both MDS and AML combined. The relapse at two years was statistically significantly higher for patients who received non-myeloablative conditioning rather than reduced-intensity conditioning (OR, 1.46, 95%CI, 1.15 - 1.85; p=0.002) and for patients with an unfavorable/poor-risk cytogenetic profile (OR, 1.57, 95%CI, 1.04 - 2.35; p<0.03). Patients with early MDS had a lower two-year relapse than patients with advanced MDS (OR, 0.43, 95%CI, 0.26 - 0.714; p<0.001). Patient age did not impact relapse.

TABLE 18: Disease-free survival for patients forty years of age and older who received HSCT for MDS according to age group (from McClune, et al., 2010).

	40-54 years	55-59 years	60-64 years	65 years and older
%Disease-free survival (95% CI)				
1-year	44 (37-51)	40 (32-49)	43 (34-52)	42 (29-56)
2-year	39 (32-46)	32 (24-40)	35 (27-45)	36 (23-49)
No statistically significant differences seen.				

Multivariate analysis was performed for both MDS and AML combined. Disease-free survival was adversely affected for patients with an unfavorable/poor-risk cytogenetic profile (OR, 1.27, 95%CI, 1.01 - 1.61; p=0.05) and greater HLA disparity (p=0.05 across the group). Patient age did not impact disease-free survival.

TABLE 19: Overall survival at 2 years for patients forty years of age and older who received HSCT for MDS according to age group (from McClune, et al., 2010).

	40-54 years	55-59 years	60-64 years	65 years and older
%Overall survival at 2 years (95% CI)				
	42 (35-49)	35 (27-43)	45 (36-54)	38 (25-51)
No statistically significant differences seen.				

Multivariate analysis was performed for both MDS and AML combined. Overall survival at two-years was adversely affected for patients with a lower Karnofsky Performance Score (i.e., a more debilitated patient; OR, 1.63, 95%CI, 1.21 - 2.20; p=0.001) and for patients with an unfavorable/poor-risk cytogenetic profile (OR, 2.01, 95%CI, 1.39 - 2.91; p<0.001). Patient age did not impact overall survival at two-years.

The authors noted that "transplantation toxicity, relapse, and survival for older adults are not significantly different than those for younger adults undergoing a similar NMA or RIC allogeneic HCT" while acknowledging "that small patient numbers may confound recognition of small differences in outcomes; however, these encouraging data help confirm the overall safety and tolerability of the procedure, even in the oldest group." The authors also noted the uncertainty that remains regarding the best conditioning regimen for allogeneic HSCT and stated that "carefully designed prospective trials are essential to determine the contribution of a specific conditioning regimen to success disease control."

The authors concluded that their study demonstrated that allogeneic HSCT preceded by nonmyeloablative or reduced-intensity conditioning "resulted in 2-year survival rates of greater than 30% in all age groups, whereas conventional chemotherapy offers almost no chance of extended survival for older patients with AML or MDS" and that the data "support active consideration of HCT in older patients." However, they also conclude that "much work remains" regarding the role and impact of novel therapies such as monoclonal antibodies and vaccines for MDS as well as the need to perform quality-of-life studies in older patients who receive an allogeneic HSCT.

Lim ZY, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. Journal of Clinical Oncology2010; 28:405-411.

This was a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT) registry database (from 1998 to 2006) on 1333 patients age fifty or older from 202 centers who received a HSCT that was preceded by either reduced-intensity conditioning (RIC) or standard myeloablative conditioning (SMC).

The FAB classification scheme was used to determine the specific subtype of MDS. Disease status was classified as either "early" (marrow blast count of less than five percent) or "advanced" (marrow blast count greater than five percent). Twenty-five percent of patients had a diagnosis of AML secondary to MDS. The cytogenetic profile for MDS was listed as either good, standard, poor or unavailable however there were sufficient cytogenetic data available for only 31% of the patients so the analysis did not include IPSS score as a variable. For the analysis the patients were divided into two age groups: fifty to sixty years or greater than sixty years. The primary outcomes reported were overall survival, nonrelapse mortality and relapse rate.

Of the 1333 total patients, 34% were older than sixty years and the median age in this group was 63 years with a range of sixty to 75. Forty-two percent of all patients had early disease while 52% had advanced disease and the disease status was unavailable for six percent. Sixty-two percent of patients received RIC. Patients who were older than sixty years were more likely to receive RIC compared to SMC (78% v. 55%; $p<0.01$) and an unrelated donor transplant compared to a related donor transplant (37% v. 32%; $p=0.03$). Patients in the fifty to sixty year age group were more likely to have advanced disease compared to early disease (significance not reported).

Patients who received RIC had a significantly lower four-year nonrelapse mortality compared to those who received SMC (32% v. 44%; HR, 0.84; $p = 0.05$). The difference in nonrelapse mortality between the two age groups was not statistically significant but was significantly higher in patients who received an unrelated donor transplant (whether HLA-mismatched or matched) compared to a related donor transplant (54% v. 40% v. 34%; $p = 0.02$).

The results of multivariate analysis showed that nonrelapse mortality at four years was significantly adversely affected by advanced disease at transplantation (HR, 1.43, 95%CI, 1.13 - 1.79; $p = 0.01$) and the use of an HLA-matched unrelated donor transplant (HR, 1.57, 95%CI, 1.10 - 2.24; $p=0.01$). The use of RIC however was significantly associated with a decrease in the hazard ratio for nonrelapse mortality (HR, 0.79, 95%CI, 0.65 - 0.97; $p = 0.03$).

Patients who received RIC had a significantly higher four-year relapse rate compared to those who received SMC (41% v. 33%; HR, 1.39; $p<0.01$). The difference in relapse rate between the two age groups was statistically significant with a higher relapse in the sixty and older group (32% v. 41%; HF, 1.32; $p = 0.02$). There was no significant difference in relapse rate among the patients who received either a related or an unrelated donor transplant.

Multivariate analysis demonstrated that the relapse rate at four years was statistically significantly higher for patients who received RIC (HR, 1.44, 95%CI, 1.13 - 1.84; $p<0.01$) and for patients with advanced disease (HR, 1.51, 95%CI, 1.18 - 1.93; $p<0.01$).

There was no significant difference in overall survival at four years between the two age groups or between patients who received RIC compared to those who received SMC. The two primary causes of death were transplant-related causes (56%) and relapse (37%).

The results of multivariate analysis showed that overall survival at four years was significantly adversely affected by advanced disease at transplantation (HR, 1.55, 95%CI, 1.32 - 1.83; $p<0.01$).

The authors addressed some of the limitations of their study including incompleteness of the registry data as well as the use of the FAB classification. If their study had used the WHO classification of MDS rather than the FAB classification then the percentage of patients initially diagnosed with AML would have increased from 25% to 41%.

According to the authors the "single most important prognostic variable in our study was the disease stage at time of transplantation, with patients with more than 5% blasts at time of transplantation having a significantly inferior RFS [relapse-free survival] and OS [overall survival]." The "other major variable influencing outcomes in our study is the choice of donor" where using an HLA-matched related donor was associated with significantly lower nonrelapse mortality compared to using an unmatched donor.

The authors concluded "that transplant physicians need to consider both age as well as the coexistence of other comorbidities in the evaluation of patient" and that currently available "comorbidity indices should be incorporated as part of transplant registry data collection forms for future studies." Furthermore, their "study suggests again that advanced age per se, should not be a contraindication for allografting in MDS" however "our data suggest that in older patients with MDS, the choice of stem-cell donor remains a point of consideration, although both types of donors result in significant long-term survival even in patients older than 60 years." In addition, it was noted that specific "questions need to be addressed with regards to" the role and toxicity of pre-transplantation chemotherapy and conditioning regimens in older patients. The authors conclude that our "study indicates that in older patients with advanced disease stage at transplantation; alternative treatment options or novel treatment regimens should be considered." "Novel immunomodulatory and disease modifying agents" were provided as examples of alternative treatment options.

5. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) Meeting was not convened on this topic.

6. Evidence-based guidelines

On February 2, 2010, the online National Guideline Clearinghouse database was searched using the terms "myelodysplastic syndrome" and "transplantation." No guidelines were found.

On February 2, 2010 the website for the Cochrane Collaboration, the National Institute for Health and Clinical Excellence, the Canadian Agency for Drugs and Technologies in Health, and the Australian Government Department of Health and Ageing were searched using the terms "myelodysplastic syndrome" and "transplantation." No guidelines were found.

National Comprehensive Cancer Network (NCCN) Guideline

CMS is aware that the NCCN publishes a clinical practice guideline titled Myelodysplastic Syndromes. (NCCN Guideline, 2009) The most recent version was released on August 26, 2009. The guideline is prepared by the NCCN Myelodysplastic Panel, which is comprised of experts in medical oncology, hematology/hematology oncology, internal medicine and/or pathology from various centers throughout the United States. The NCCN uses a "Categories of Evidence and Consensus" to classify its recommendations. There are 4 categories (1, 2A, 2B and 3) with Category 1 providing the strongest strength of recommendation. All recommendations are classified as Category 2A in the Myelodysplastic Syndromes guideline unless otherwise noted. Category 2A means that the "recommendation is based on lower-level evidence and there is uniform NCCN consensus."

The 2009 NCCN guideline notes the historical use of the FAB classification and then presents the current use of the 2008 WHO classification of MDS. This classification also includes myeloproliferative neoplasms. The guideline continues by presenting the IPSS classification system. In the Background section titled "Classification of MDS" of this NCA, Table 4 (which is a table from the 2009 NCCN guideline) presents two types of outcome data on untreated patients in each IPSS risk group: median survival in years and the number of years it would take for 25% of the MDS patients to progress to AML. These outcomes range from 5.7 and 9.4 years, respectively, for the low risk untreated patients, to 0.4 and 0.2 years, respectively, for the high risk group. The 2009 NCCN guideline remarks that both "for survival and AML evolution, the IPSS showed statistically greater prognostic discriminating power than earlier classification methods, including the FAB system." Of note, in its discussion section the 2009 NCCN guideline comments that a study by Alessandrino, et al. (2008) "retrospectively evaluated the impact of WHO classification and WPSS on the outcome of patients who underwent allogeneic HSCT. Data suggest that lower risk patients (based on WPSS risk score) do well with allogeneic HSCT with a 5-year overall survival of 80% whereas those with 5-20% marrow blast have only 25-28% 5 year overall survival." The 2009 NCCN guideline, however, uses the IPSS classification to plan treatment options.

The 2009 NCCN guideline stratifies its treatment algorithms by risk group with the low risk group (comprised of the IPSS categories Low and Intermediate-1) presented separately from the high risk group (comprised of IPSS categories Intermediate-2 and High). For the Low and Intermediate-1 categories the 2009 NCCN guideline recommends that HSCT should generally be considered after numerous other types of generally low-intensity treatments have been administered unsuccessfully such as supportive care with transfusions, antibiotics, iron chelation and growth stimulating hormones (e.g., erythropoietin) and various types of chemotherapy including hypo-methylating agents, biologic response modifiers and immunosuppressive agents. Participation in a clinical trial was the other recommendation for patients in this low risk group who have disease that is unresponsive to low-intensity treatment.

For the high risk group (comprised of IPSS categories Intermediate-2 and High) the 2009 NCCN guideline recommends high-intensity treatment consisting of intensive chemotherapy or allogeneic HSCT where allogeneic "HSCT from a HLA-matched sibling donor is a preferred approach for treating a portion of patients with MDS, particularly those with high-risk disease." The algorithm indicates that intensive chemotherapy should be administered if the patient is not a transplant candidate with an available donor and a sufficiently low marrow blast count. A patient’s treatment preference, age, performance status, major co-morbid conditions, psychosocial status and the availability of caregiver are also factors that should be weighed to determine eligibility for transplantation. If the patient is not a high-intensity treatment candidate then non-intensive treatment with chemotherapy or a clinical trial is recommended.

The 2009 NCCN guideline discusses the issue of myeloablative conditioning versus the use of reduced intensity conditioning (RIC) by noting that myeloablative conditioning regimens can be used for younger patients while non-myeloablative conditioning or RIC "is preferable in older individuals." Based on the results from clinical studies the guideline states that a patient’s "age and disease status generally dictate the type of conditioning to be utilized," where "disease status" consists of the blast count. Additionally, variations should "be considered by the individual transplant physician based on these features and the specific regimen utilized at that center."

Finally, the guideline concludes with the following recommendation for additional research: "Progress toward improving management of MDS has occurred over the past few years and more such advances are anticipated using these guidelines as a framework for coordination of comparative clinical trials."

7. Professional Society Position Statement

The website for each of the following organizations was searched for a position statement: the National Marrow Donor Program, the American Society for Blood and Marrow Transplantation, the American Cancer Society, the American Cancer Society Cancer Action Network, the AABB, the American Society of Hematology, the American Society of Clinical Oncology, the Aplastic Anemia and MDS International Foundation, the Blood and Marrow Transplant Information Network, the National Bone Marrow Transplant Link, the Bone Marrow Foundation, and the Leukemia and Lymphoma Society.

The only position statement found during this search was from the American Society for Blood and Marrow Transplantation (ASBMT; http://www.asbmt.org/NR/rdonlyres/589BEE9A-DF10-4EC5-B9DD-5054FD647AF5/0/BBMT_published_MDS_PositionStatement.pdf). This statement recommends early HSCT for patients with high risk disease (noted as Intermediate-2 on the IPSS score) at diagnosis who also have a suitable donor and qualify for a transplant center's transplant protocol as well as for patients with low risk disease at diagnosis (noted as Intermediate-1 on the IPSS score) but "who have poor prognostic features not included in the IPSS (e.g., older age, refractory cytopenias)." Of note, ASBMT is one of the requestors for this NCD.

8. Public Comments

CMS uses the initial public comments to inform its proposed decision. Public comments that contain personal health information will not be made available to the public. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

Initial 30-day comment period

We received two hundred and sixty-four comments, all in favor of coverage for HSCT for MDS, with some of those comments citing published evidence. We reviewed the comments in their entirety,including reviewing all referenced literature submitted in part as comments from professional organizations. The commenters were unanimous in their support as well as consistent in the substantive issues they represented throughout the comments. In general, they referred to the clinical benefits of HSCT and reflected like concerns related to the current lack of national coverage.

The majority of comments were submitted by beneficiaries, relatives and friends of beneficiaries, and physicians and other health professionals. Comments also were submitted by many hospitals, including some major cancer hospital centers such as the Fred Hutchinson Cancer Research Center, Dana Farber Cancer Institute, Memorial-Sloan Kettering Cancer Center, Cleveland Clinic, H. Lee Moffitt Cancer Center, and MD Anderson Cancer Hospital.

A Member of Congress submitted comments in support of national coverage for HSCT. Some major societies and organizations submitted comments also in support of coverage, including the America's Health Insurance Plans (AHIP), The Leukemia and Lymphoma Society, the American Society for Apheresis (ASFA), the Alliance of Dedicated Cancer Centers ("the Centers"), and the Aplastic Anemia and MDS International Foundation.

A significant number of organizations and hospitals, including numerous cancer centers, remarked on data collection and submission mandates which they believe support national coverage through better tracking mechanisms, such as the federal reporting requirements established under the Stem Cell Therapeutic and Research Act of 2005 (The Act established the Stem Cell Therapeutic Outcomes Database (SCTOD) which enables CMS to track beneficiary outcomes). The ability to monitor quality and track outcomes through these established mechanisms was cited frequently in the comments. Some commenters referred to a proposed bill HR 1230 which a few believe allows national coverage for HSCT. In fact, the bill proposes the establishment of a National Acquired Bone Marrow Failure Disease Registry and advisory committee, as well as the award of grants to collect, analyze and report data.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a) (1) (A) of the Act.

In addition to section 1862(a) (1) (A), a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a) (1) (E), provides, in pertinent part, that:

(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
. . .
(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]
. . .

Section 1142 describes the authority of the AHRQ.

Under the authority of § 1862(a)(1)(E), Medicare may cover under coverage with evidence development/coverage with study participation (CED/CSP) certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A), and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. CMS has described CED/ in greater detail in guidance document available at http://www.cms.gov/mcd/ncpc_view_document.asp?id=8. CED allows CMS to provide coverage based on a determination that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise.

Under section 1142, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.

For some items or services, CMS may determine that the evidence is preliminary and not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A), but, if the following criteria are met CED/ might be appropriate:

- The evidence includes assurance of basic safety;
- The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and
- There are significant barriers to conducting clinical trials.

These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

Regarding these 3 criteria:

1. The varying prognosis for MDS needs to be weighed against the significant chance for morbidity and mortality after HSCT. In the studies evaluated, the health outcomes examined (treatment-related mortality, non-relapse mortality, progression-free survival, relapse rate and overall survival) attest to the significant morbidity and mortality associated with HSCT. Martino, et al. (2006) showed a nonrelapse mortality rate of 22% and a relapse rate of 45% three years after HSCT for patients who received reduced-intensity conditioning. Lim, et al. (2010) showed a four-year nonrelapse mortality rate of 32% and a relapse rate of 41% three years after HSCT for patients who received reduced-intensity conditioning. Although the individual rates of these two health outcomes may differ between studies, a reduction in nonrelapse mortality and an increase in relapse rate in patients given reduced-intensity conditioning appear to be a consistent finding in the literature as noted in McClune, et al. (2010) and Lim, et al. (2010). Results from these two studies also demonstrated that this relationship occurs in patients 65 years and as older as well as in younger patients. However, the evidence also points to a decreased health benefit from HSCT with increasing patient age and with worsening disease.

   While allogeneic stem cell transplantation has been performed for years and has known risks (including death), the risks may be evaluated by the patient and accepted in the context of a clinical study that include additional protections and safety measures for beneficiaries.

2. Several authors, as well as professional societies quoted in this proposed decision memorandum have cited the potential for allogeneic stem cell transplantation to be "curative" for MDS, albeit in a limited proportion of patients. Given the poor prognosis for older patients with MDS and who are in the IPSS High risk category as well as the lack of treatment alternatives other than supportive care, CMS believes that HSCT has the potential to provide a health benefit. For older patients with MDS who are in the IPSS Low risk category, but who have disease that has become refractory to standard treatment, and who have a poor prognosis and lack treatment alternatives other than supportive care, CMS believes that HSCT has the potential to provide a health benefit.
3. Despite the repeated call in the clinical literature for further research, as noted in numerous published articles including Oliansky, et al. (2009), Laport, et al. (2008) and McClune, et al. (2010) the evidence review is notable for an absence of comparative trials of treatment for MDS. Two commonly stated significant barriers to conducting comparative LP clinical trials are the poor prognosis for patients with High risk MDS prior to HSCT and the commonly-held belief in the transplant community (as noted by several authors and professional societies quoted in this memorandum) that HSCT is the only "cure" for MDS.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future national coverage decision that would focus on whether the item or service should be covered by Medicare under 1862(a)(1)(A). Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study. Based on the legal framework set forth above, this section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions.

CMS asked the following question when analyzing the evidence: *Is the evidence adequate to conclude that beneficiaries with a diagnosis of MDS would experience improved health outcomes with a HSCT compared to beneficiaries whose management does not include HSCT?*

In our review, we evaluated one review article, one guideline and five published peer-reviewed articles that addressed the use of HSCT in patients with MDS including a decision analysis, 3 retrospective multicenter studies and one prospective multicenter study. The systematic review of the literature by Oliansky, et al. (2009) synthesized the results of 46 original papers, generally case series or prospective cohort studies, many of which focused on a specific, individual aspect of performing a HSCT such as the optimal timing of transplantation, the role for reduced-intensity conditioning versus standard myeloablative conditioning or the use of bone marrow stem cells versus peripheral blood cell stem cells rather than our question of interest. In addition, the study design commonly employed in the studies (case-control or cohort studies) resulted in evidence that the authors rated as of lower quality than evidence obtained from controlled clinical trials (consistent with our hierarchy of evidence, Appendix A). The resultant recommendations were therefore of lesser strength. We did not find any study that compared the use of HSCT to other types of therapies such as supportive care, intensive chemotherapy, non-intensive chemotherapy or some combination in patients with MDS who are 65 or older. This evidence base does not support unrestricted coverage of HCST for patients with MDS.

Patients with MDS who are in the Low or Intermediate-1 risk category (a low risk group in the IPSS classification system) have 5.7 or 3.5 year median survival in the absence of therapy, respectively (Table 4). These patients also have a 25% chance of progression to AML in 9.4 years or 3.3 years, respectively (Table 4). Regardless of age, the 2009 NCCN guideline recommends that patients in the low risk group receive low intensity therapy unless their disease becomes refractory to treatment. For refractory anemia, this is associated with a shortened survival and a shorter time to progression to AML, as demonstrated by Malcovati, et al. (2005) at which time high-intensity treatment with intensive chemotherapy or HSCT is warranted. Since most patients of Medicare age will be ineligible for intensive chemotherapy due to co-morbidities and/or generally poor health status, HSCT may be their only potential option. Oliansky, et al. (2009) recommend HSCT "for selected patients with a Low or Intermediate-1 risk IPSS score at diagnosis who have poor prognostic features not included in the IPSS (i.e., older age, refractory cytopenias, etc.)."

Patients with MDS who are in the IPSS Intermediate-2 or High risk category (a high risk group) have a median survival of 1.1 or 0.4 years, respectively, in the absence of treatment and a 25% chance of progression to AML in 1.1 years or 0.2 years, respectively (Table 4). For these patients low intensity therapy is ineffective. The 2009 NCCN guideline recommends that these patients start with high-intensity treatment where patients of Medicare age experience the same barriers to intensive chemotherapy and find that HSCT is their only option with improved health outcomes. Oliansky, et al. (2009) recommend "early SCT for patients with an IPSS score of Intermediate-2 or High risk at diagnosis, who have a suitable donor, and meet the transplant center’s eligibility criteria."

Cutler, et al. (2004) presented the results of a retrospective, decision-modeling study that used several observational databases to compare a cohort of patients who received a HSCT to a cohort of patients who did not receive HSCT. The study demonstrated a longer median survival for the non-HSCT cohort. While this study addressed our question, as noted in Appendix A, the reliance on observational data and the retrospective nature of the study design limit the quality of the evidence. In addition, having been published in 2004 and therefore before the common use of reduced-intensity conditioning, the evidence was from patients who received only myeloablative conditioning. This aspect of the study design limits the applicability of the evidence to standard practice today, especially for Medicare-age patients.

Laport, et al. (2008) presented the results of a case series study of patients who received HSCT. This was a multicenter study with a different treatment protocol for each center, which can significantly decrease the controlled nature of the study and adversely impact the quality of the evidence. The remaining three articles (Martino, et al., 2006; McClune, et al., 2010; Lim, et al., 2010) each provided the results of a retrospective analysis of an observational database of patients who received HSCT and therefore, were impacted by the same inherent methodological shortcomings, as noted above for Cutler, et al. (2004).

Another overall weakness was the paucity of evidence regarding the use of HSCT patients with MDS who are 65 years and older. This was due to the blanket ineligibility assigned to this age group until relatively recently. With the recent introduction of non-myeloablative conditioning or reduced-intensity conditioning during the past decade, studies have increasingly included patients who are 65 years and older. However at this time the size of the database is still small.

Despite the lack of evidence in patients 65 years of age and older, CMS recognizes that evidence in patients who are in their late fifties or early sixties can be extrapolated to some degree to <u>younger</u> Medicare-age patients. For older patients, however, CMS believes that the onset of co-morbidities and the general decline in health status in general increase significantly enough as a person progresses throughout the decades to render evidence from fifty year olds less representative of patients who are in their seventies or eighties, especially when considering a particularly intensive and potentially risky therapy such as HSCT.

Given the relatively recent advent of reduced-intensity and non-myeloablative conditioning regimens, another concern is the lack of an optimal conditioning regimen. The heterogeneity of regimens comprised of varying combinations and doses of pharmaceutical agents, biopharmaceutical agents and radiation therapy that have been and continue to be employed in transplantation center protocols (which is a reflection of the general heterogeneity within the practice of transplantation medicine) limits the ability to compare health outcomes across individual studies.

Given the weaknesses of and our concerns about the evidence as noted above, CMS believes that HSCT shows promise to provide a health benefit for Medicare-age patients with MDS, but that the available evidence is not adequate to determine that allogeneic hematopoietic stem cell transplantation improves health outcomes in Medicare beneficiaries with MDS. CMS determines that the evidence does not demonstrate that the use of allogeneic HSCT improves health outcomes in Medicare beneficiaries with MDS and thus, is not reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act. CMS proposes, however, thatevidence is promising for the use of allogeneic HSCT for MDS and supports additional research for this service under 1862(a)(1)(E) (consistent with section 1142 of the Act) and our CED policy.

Coverage with Evidence Development

As we noted above, CMS believes that that the available evidence does not support a conclusion that the use of allogeneic HSCT improves health outcomes in Medicare beneficiaries with MDS. Therefore, we are proposing that allogeneic HSCT for MDS is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. However, we do believe the available evidence suggests that allogeneic HSCT for MDS is reasonable and necessary under §1862(a)(1)(E) of the Social Security Act through CED. Thus, we are proposing that allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome is only covered by Medicare in the context of a prospective controlled clinical study.

A clinical study seeking Medicare payment for treating allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome pursuant to CED must address one or more aspects of the following questions:

1. Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?
2. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do IPSS score, patient age, cytopenias and comorbidities predict the following outcomes:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?
3. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:

- relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR Parts 50 and 56.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

   (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

CMS acknowledges the role of the accreditation organizations in facilitating the development of and maintaining the presence of high quality policies, procedures and practices in the field of transplantation. Both the NMDP and the FACT-JACIE have established provider and facility standards as noted previously in the Introduction to section VII.

The facility (i.e., transplant center) participation criteria are set forth by the NMDP. These include requirements for the facility as well as the personnel and transplant team, including physician qualifications and board certification requirements. There are specific standards related to support services, policies and procedures, patient advocacy and administrative compliance rules. The NMDP also established a volume requirement mandate that requires that the applicant center has performed ten allogeneic transplants for at least ten different patients in 24 months or for twenty different patients within the last twelve months. The NMDP standards are specific to unrelated allogeneic transplantation and apply to all donor recruitment, donor screening, and collection storage processing release and transplantation and administration of hematopoietic stem cells facilitated through the NMDP.

The key clinical program standards are set forth by the FACT-JACIE, two organizations that maintain separate and parallel accreditation processes, but have jointly established international standards related to the primary functions within a transplant program: the clinical program, collection facility and processing facility. The FACT-JACIE standards provide minimal guidelines for programs facilities and individuals. These include clinical program, personnel quality management, policies and procedures, clinical research and data management. The clinical program accreditation requires that there be ten new allogeneic HSCT patients per year and the requirement must be met during the two month period immediately preceding the application.

In addition, a federally mandated outcomes data collection for HSCT for MDS captures data on all U.S. recipients, including Medicare beneficiaries and was enacted in accordance with the Stem Cell Therapeutic and Research Act of 2005 (U.S. Public Law 109-129). The CIBTMR was awarded a contract by HRSA (Health Resources and Services Administration) to administer the Stem Cell Outcomes Database (SCTOD). For all U.S. allograft recipients, a standard dataset must be submitted to the CIBTMR. The SCTOD collects data on the allogeneic transplants in order to increase safety, efficacy and availability of HSCT. All participating centers provide a dataset of their recipients' pre-and post- transplant at 100-day, 6-month, and annual interviews. The data set known as the transplant essential data (TED) encompasses in part, both the dataset required for submission to SCTOD as well as for the FACT-JACIE accreditations. Through the CIBTMR a worldwide network of HSCT centers currently share data on HSCT outcomes and maintains a clinical database with information for more than 280,000 recipients.

The role of the statutorily-mandated data collection program administered by CIBMTR is and will continue to be critically important. The collection and analysis of data on patients with MDS who are of Medicare age and who receive a HSCT will permit the reassessment and revision of this coverage policy.

IX. Conclusion

CMS believes that that the evidence does not demonstrate that the use of allogeneic hematopoietic stem cell transplantation (HSCT) improves health outcomes in Medicare beneficiaries with myelodysplastic syndromes (MDS). Therefore, we are proposing that allogeneic HSCT for MDS is not reasonable and necessary under §1862(a) (1) (A) of the Social Security Act. However, we do believe the available evidence suggests that the use of allogeneic HSCT in Medicare beneficiaries with MDS is reasonable and necessary under §1862(a) (1) (E) of the Social Security Act through Coverage with Evidence Development (CED). Thus, we are proposing the following decision:

Allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes is covered by Medicare only in the context of a prospective controlled clinical study that meets the following standards:

A clinical study seeking Medicare payment for treating allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome pursuant to Coverage with Evidence Development (CED) must address one or more aspects of the following questions:

1. Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?
2. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do IPSS score, patient age, cytopenias and comorbidities predict the following outcomes:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?

3. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

Proposed revisions to sections 90-160.25 of the NCD Manual are available in Appendix C. We are requesting public comments on this proposed determination pursuant to section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

APPENDIX A

General Methodological Principles of Study Design
(Section VI of the Proposed Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix B

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Appendix C

DRAFT

Medicare National Coverage Determinations Manual

Chapter 1, Part 2 (Section 110.8.1.)
Coverage Determinations

Table of Contents
(Rev.)

A. General

Myelodysplastic Syndrome (MDS) refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These bone marrow disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics.

The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow. There are three "families" of cells commonly found in the blood: red cells, white cells and platelets. Most patients present with signs or symptoms of anemia (due to abnormally lowered cell counts), which can be accompanied by infection (due to abnormally low white cell counts) and/or bleeding (due to abnormally low counts of platelets). However, some patients may be asymptomatic.

Failure of the bone marrow to produce mature healthy cells is typically a gradual process therefore MDS is not necessarily a rapidly terminal disease. The life expectancy may be measured in months to years and will vary considerably depending on the severity of the specific disorder, the patient’s ability to withstand treatment and the patient’s responsiveness to treatment. The worst case scenario is the transformation of MDS to acute myeloid leukemia (AML), which can occur in approximately thirty percent of patients with MDS. AML is an aggressive type of cancer that often fails to respond to treatment and has a high mortality rate.

Allogeneic hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cells are multipotent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells,can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis—a process by which cells that are unneeded or detrimental self destruct. Stem cell transplantation is a process in which stem cells come from either a patient's (autologous) or donor's (allogeneic) peripheral blood for intravenous infusion. Autologous Transplant patients receive their own stem cells. Allogeneic transplant patients receive stem cells from a parent or sibling, or unrelated donor. Allogeneic stem cell transplantation is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT is commonly used in cancer treatment in conjunction with very high doses of chemotherapy and/or radiation therapy to make the chemotherapy regimen possible.

B. Conclusion

CMS believes that the evidence is inadequate to conclude that the use of allogeneic hematopoietic stem cell transplantation (HSCT) improves health outcomes in Medicare beneficiaries with myelodysplastic syndromes (MDS). Therefore, we are proposing that Hematopoietic Stem Cell Transplantation for MDS is not reasonable and necessary under 1862(a) (1) (A) of the Social Security Act. However, we do believe the available evidence suggests that allogeneic HSCT for MDS is reasonable and necessary under §1862(a) (1) (E) of the Social Security Act through Coverage with Evidence Development (CED). Thus, we are proposing the following decision:

"Allogeneic HSCT is covered for beneficiaries who have MDS who are candidates for this procedure pursuant to CED in the context of a prospective controlled clinical study.

Medicare payment for these beneficiaries will be restricted to patients enrolled in a prospective comparative clinical study. In accordance with the Stem Cell Therapeutic and Research Act of 2005 (US Public Law 109-129) a standard dataset is collected for all allogeneic transplant patientsin the United States by the CIBTMR. The elements in this dataset, comprised of 2 mandatory forms plus one additional form, encompass the information we require for a study under CED.

A prospective clinical study seeking Medicare payment for treating a beneficiary with allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes pursuant to Coverage with Evidence Development (CED) must meet all of the following conditions:

The clinical study must address one or more aspects of the following questions:

1. Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?
2. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?
3. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:
    - relapse free mortality,
    - progression free survival,
    - relapse, and
    - overall survival?

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The clinical research study must adhere to the following standards of scientific integrity and relevance to the Medicare population. The clinical research study should have the following features:

- It should be a prospective longitudinal study with clinical information from the period before HSCT and short and long term follow up information.
- Outcomes should be measured and compared among pre-specified subgroups within the cohort.
- The study should be powered to make inferences in subgroup analyses.
- Risk stratification methods should be used to control for selection bias. Data elements to be used in risk stratification models should include:

Patient selection:
Risk stratification methods should be used to control for selection bias. Data elements to be used in risk stratification models should include:

- Patient Age at diagnosis of MDS and at transplantation
- Date of onset of MDS
- Disease classification (specific MDS subtype at diagnosis prior to preparative /conditioning regimen using WHO classification). Include presence/absence of refractory cytopenias.
- Co morbid conditions

- IPSS score (and WPSS score, if applicable) at diagnosis and prior to transplantation
- Score immediately prior to transplantation and one year post transplantation
- Disease assessment at diagnosis at start of preparative regimen and last assessment prior to preparative regimen Subtype of MDS (refractory anemia with or without blasts, degree of blasts, etc.)
- Type of preparative/conditioning regimen administered (myeloabalative, non-myeloablative, reduced –intensity conditioning)
- Donor type
- Cell Source
- IPSS Score at diagnosis

Facility Criteria

- Facilities must be accredited by the NMDP or the FACT-JACIE.
- Facilities must meet either the volume requirements established by the NMDP or FACT-JACIE. This means they must have least one member of the allogeneic HSCT team with experience performing at least 10 allogeneic transplants for at least ten different patients in 24 months (NMDP) or for twenty different patients in the last 12 months (FACT-JACIE).
- Facilities must submit the required transplant essential data to the SCTOD.

B. Nationally Covered Indications

The following uses of allogeneic bone marrow transplantation are covered under Medicare:

1 Leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary. (effective for services performed on or after August 1, 1978,)

2. Severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome (effective for services performed on or after June 3, 1985)

The following uses of allogeneic hematopoietic stem cell transplantation are covered under Medicare:

Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) (effective for services performed on or after August 10, 2010) in the context of a prospective controlled clinical study.

C. Nationally Non-Covered Indications

- Allogeneic stem cell transplantation is not covered as atreatment for multiple myeloma (Effective for services performed on or after May 24, 1996)"

D. Other

- CMS has determined that the available evidence does not adequately support coverage for individuals other than in the group described above in (B).
- (This NCD last reviewed November 2005)

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